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CARDIORESPIRATORY DISTURBANCES ASSOCIATED WITH INFECTIVE FEVER IN MAN
Studies of Ethiopian Louse-Borne Relapsing Fever

By

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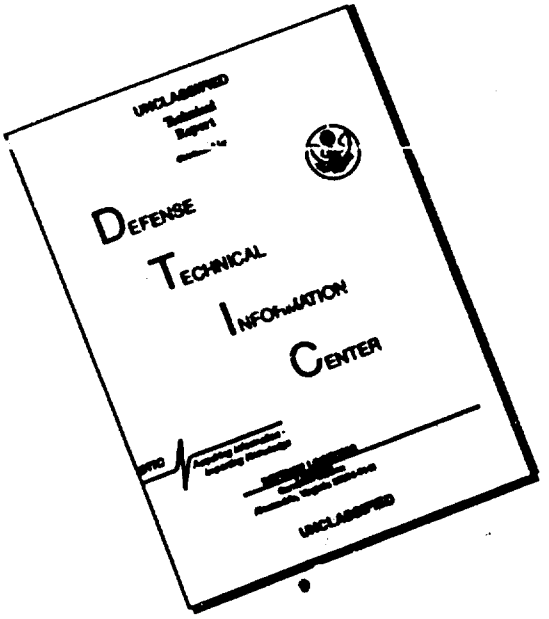

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2. Following treatment with tetracycline a febrile Jarisch-Herxheimer-like reaction developed which showed the phases described in artificially-induced endotoxin fever.

3. During the chill phase body temperature, metabolic rate and pulmonary ventilation increased. Despite alveolar hyperventilation pulmonary venous admixture was high. Cardiac output, heart rate and systemic arterial pressure increased but pulmonary arterial pressure decreased.

4. During the flush phase systemic arterial pressure fell and remained low for many hours due to reduced vascular resistance, but pulmonary arterial pressure and inflow resistance increased. Small increases in glucose, lactate, and pyruvate concentrations were prevented by inhaling oxygen.

5. Stimulation of metabolic rate, ventilation and cardiac output during the reaction was not due simply to increased body temperature, hypoxia, or acidosis but was probably attributable to spirochaetal endotoxin.

6. Limitation of pulmonary oxygen diffusion may have been responsible for the impaired pulmonary oxygen uptake in these patients.

7. During the prolonged flush phase a greatly increased cardiac output is necessary to maintain systemic arterial pressure because of the very low vascular resistance. Prevention of extracellular fluid volume depletion, early detection and prompt treatment of cardiac failure and oxygen therapy may reduce fatalities during this critical period but hydrocortisone in large doses failed to reduce the severity of the reaction.

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SUMMARY

1. Nineteen patients with louse-borne relapsing fever were studied in Addis Abeba (altitude 2285 m).

2. Following treatment with tetracycline a febrile Jarisch–Herxheimer-like reaction developed which showed the phases described in artificially-induced endotoxin fever.

3. During the chill phase body temperature, metabolic rate and pulmonary ventilation increased. Despite alveolar hyperventilation pulmonary venous admixture was high. Cardiac output, heart rate and systemic arterial pressure increased but pulmonary arterial pressure decreased.

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5. Stimulation of metabolic rate, ventilation and cardiac output during the reaction was not due simply to increased body temperature, hypoxia, or acidosis but was probably attributable to spirochaetal endotoxin.

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7. During the prolonged flush phase a greatly increased cardiac output is necessary to maintain systemic arterial pressure because of the very low vascular resistance. Prevention of extracellular fluid volume depletion, early detection and prompt treatment of cardiac failure and oxygen therapy may reduce fatalities during this critical period but hydrocortisone in large doses failed to reduce the severity of the reaction.

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Louse-borne relapsing fever (LBRF) is caused by *Borrelia recurrentis* spirochaetes. The mortality may be as great as 70% among untreated cases but is reduced by treatment with arsenicals or antibiotics. Unfortunately, the doses of these drugs required to eliminate spirochaetes from the blood and prevent relapses frequently result in severe febrile reactions reminiscent of the Jarisch–Herxheimer reaction of syphilis (Robertson, 1932; Taft & Pike, 1945). Occasionally patients die during the reaction to treatment, either in convulsions at the peak of fever or in a state of circulatory collapse several hours later (Wolff, 1946).

Currently, the world's major endemic focus for LBRF is in the Ethiopian highlands. Parry, Bryceson & Leithead (1967) and Schofield, Talbot, Bryceson & Parry (1968) working in Addis Abeba found that a striking febrile reaction almost invariably followed treatment with tetracycline or penicillin. The four phases recognized by Altschule, Freedberg & McManus (1945) in the response to endotoxin injection can be identified in this reaction. After a *prodromal phase* of about 1 h following intravenous injection of 250 mg tetracycline there is a *chill phase* lasting 10–30 min during which body temperature, blood pressure, and pulse and respiratory rates increase. Blood pressure falls markedly during the prolonged *flush phase*. In most cases a *phase of defervescence* or recovery follows, but two of Parry's patients died at this stage. Observation of these dramatic events prompted the present studies. Our object was to discover the physiological abnormalities in patients with LBRF, both before treatment and during the febrile reaction which follows tetracycline, in the hope that such information might lead to improved clinical management.

Physiological changes in patients with infective fever have rarely been investigated (Cranston, 1959). Since the febrile reaction which follows tetracycline treatment in LBRF is remarkably predictable in its timing and uniform in its intensity it provides an unusual opportunity for the study of infective fever in man.

METHODS

Patients

During the autumn of 1968 nineteen men, in whom the diagnosis of LBRF had been confirmed by finding *Borrelia* spirochaetes in the blood, were studied in Princess Tsehai Memorial Hospital, Addis Abeba which is 2285 m above sea level (average barometric pressure 582 mmHg). They consented to treatment and investigation.

Plan of the five studies

The six patients in *Study* 1 were investigated throughout their 3 day hospital admission to establish the pattern of physiological disturbances in LBRF before and during the febrile reaction which follows treatment with tetracycline.

Studies 2–5 were accessory studies designed to amplify the results of Study 1 and to discover the causes of the observed physiological changes. In *Study* 2, which involved three patients, the object was to obtain further information about the early stages of the reaction to treatment. *Study* 3 investigated in two patients the effects of large doses of hydrocortisone on the reaction to treatment, while *Study* 4 was concerned with the effects of oxygen therapy in four patients. Finally, in *Study* 5 the acid-base composition of lumbar cerebrospinal fluid (CSF) was measured in four patients in order to discover whether there was a CSF acidosis to explain the observed respiratory stimulation.

Procedure.

Study 1: After clinical assessment forced expired volume in the first second (FEV_1) and vital capacity (VC) were measured with a McDermott bellows spirometer and peak expiratory flow (PEF) with a Wright peak flow meter with the patient sitting upright. All subsequent measurements were made while the patients were supine. Electrocardiogram (ECG) leads were attached. Rectal and forehead and right forearm skin temperatures (T_R, T_H, T_A) were measured continuously with an electronic thermometer (McDonnel, London; type MC3 incorporating Yellow Spring YS1K thermistors) checked against a Beckman thermometer.

A PE 60 polyethylene catheter 22 cm long was inserted into the left brachial artery at the antecubital fossa using a modification of the Seldinger percutaneous technique (Berneus *et al.*, 1954). The catheter was flushed with heparin-saline solution and was connected to a saline manometer. An OPP 160 polyethylene catheter 90 cm long was introduced into the right side of the heart through a left antecubital vein using the percutaneous technique and was also connected to a saline manometer. In five patients the catheter was advanced into the pulmonary artery. Brachial and pulmonary arterial mean pressures ($\bar{P}_{BA}$, $\bar{P}_{PA}$) were read from the manometers using the sternal angle, which was assumed to be 5 mmHg above zero pressure, as reference point.

At intervals throughout the study 3-min collections of expired gas were made and simultaneously, arterial and mixed venous blood (from the pulmonary artery or right ventricle) was sampled through the indwelling catheters. Immediately before and after these collections intravascular pressures and body temperatures were measured. During the collections heart rate (HR) was recorded on the ECG and respirations were counted. After each gas collection further samples of arterial blood were taken for estimation of glucose, lactate, pyruvate and haemoglobin (Hb) concentrations and haematocrit (PCV).

The arterial and mixed venous blood samples were analysed for oxygen tension (Pa,O_2, $P\bar{v},O_2$), carbon dioxide tension (Pa,CO_2, $P\bar{v},CO_2$), pH (pHa, $pH\bar{v}$), oxygen saturation (Sa,O_2, $S\bar{v},O_2$), oxygen content (Ca,O_2, $C\bar{v},O_2$) and bicarbonate concentration (HCO_3^-a, $HCO_3^-\bar{v}$).

The first expired gas collection was made before treatment when the patients had rested for 30 min after intravascular catheterization. 250 mg of tetracycline ('Bristacin-A', Bristol Laboratories) were then given by intravenous injection. (This batch of tetracycline had been found to be non-pyrogenic after intravenous injection in four control subjects.) About 1 hour after injection rigors began in all cases: these were the most definite features of the reaction and were used to time subsequent events. The second collection was made 5–15 min after rigors had started. Further collections were made 2, 4, 6, and 8 h later, on the next morning at about 18 h after the rigors and finally, on the third day of admission.

After the expired gas collection on the second day of admission the patients breathed 100% O_2 for 45 min: arterial and mixed venous Po_2, Co_2 and Pco_2 were then measured to allow calculation of residual shunt ($\dot{Q}s/\dot{Q}t$). The brachial and right heart catheters were then withdrawn. On the third day of admission brachial arterial blood was sampled by needle puncture. Spirometry and chest radiography were repeated on the second or third days of admission in some cases.

In *Study* 2 the procedure and measurements were the same as in Study 1 but additional collections of expired gas and samples of blood were taken shortly before or after the rigors. In *Study* 3 hydrocortisone sodium phosphate ('Efcortisol', Glaxo) in a concentration of 4 g/l of

isotonic saline was given by continuous intravenous infusion for 4 h starting 1 h before tetracycline injection. The dose was 20 mg kg^{-1} h^{-1}. The procedure and measurements were the same as in Study 1. In *Study* 4 a high concentration of O_2 (nominally 100%) was given by mask starting 1 h before tetracycline injection and continuing for 4 h after rigors had ended. The procedure and measurements were the same as in Study 1: O_2 therapy was stopped 15 min before each expired gas and blood collection and was restarted immediately afterwards. This allowed measurement of blood gases while the patients breathed air rather than a higher, uncertain concentration of O_2. In *Study* 5 lumbar CSF and brachial artery blood were sampled simultaneously over a 2–3 min period before treatment. The CSF was analysed for P_{CO_2}, pH, HCO_3, protein, glucose and cells. Arterial blood, which was sampled again during the rigors following tetracycline treatment, was analysed for P_{O_2}, P_{CO_2}, pH and HCO_3^-.

Analytical techniques

Blood gas and acid-base measurements. Mixed venous and arterial blood was sampled anaerobically in heparinized glass syringes. *Blood gas tensions* and *pH* were measured within 15 min of sampling using Radiometer electrodes maintained at $37 \pm 0{\cdot}05°$ and calibrated between samples with three gas mixtures which had been analysed with a Lloyd-Haldane apparatus and standard buffer solutions. Mean difference between duplicate readings: P_{CO_2} = 0·0015 mmHg, SD = 0·52, n = 270; P_{O_2} = 0·0177 mmHg, SD = 0·74, n = 254. *Blood oxygen content* was measured by a modification of the method of Linden, Ledsome, & Norman (1965), calibrated by direct comparison with the manometric method of Van Slyke & Neill (1924). Mean difference between duplicate readings of C_{O_2} = 0·0310 ml O_2 STP/100 ml blood, SD = 0·54, n = 168. *Blood oxygen saturation* was estimated by the haemoreflector (Kipp, MO1) method (Zijlstra, 1958). Mean difference between duplicate readings of S_{O_2} = 0·0212% sat, SD = 1·06, n = 33 for mixed venous samples (S_{O_2} 40–70%) and 0·0011% sat, SD = 0·51, n = 87 for arterial samples (S_{O_2} 70–100%). *Plasma carbon dioxide content* was measured using the Natelson micromanometric Van Slyke method (Scientific Industries, model 600). Bicarbonate concentration was calculated by subtracting physically dissolved CO_2.

Measurement of arterial glucose, lactate, and pyruvate concentrations. Blood *glucose* was estimated by a glucose oxidase/peroxidase method (Schweizerhall, Basel, Switzerland). Blood for *lactate* estimation was sampled anaerobically in less than 10 s and was immediately deproteinized with perchloric acid. Aliquots were analysed for lactic acid using an enzymatic method (Sigma Chemical Company No. 825). *Pyruvate* was also determined by an enzymatic method (Sigma Chemical Company No. 725). Optical densities were measured by an SP500 spectrophotometer (Hilger-Watts).

Collection and analysis of expired gas. The respiratory circuit consisted of a Siebe Gorman valve box (dead space 55 ml, resistance <1 cm H_2O at 3 l/s) connected through wide-bore tubing to a 50 l Douglas bag. After the circuit had been flushed with expired gas for 5–10 min the timed collection was made. A sample of known volume was removed for analysis in the Radiometer electrodes and the volume of the remaining expirate was measured with a gas meter whose accuracy was $\pm 1{\cdot}3\%$ at flows of <180 l/min.

Temperature corrections

Rectal temperature was considered to be the most practicable measure of 'body core' temperature in these studies (Grimby, 1962; Cranston, 1966; Warrell, 1969). Lung gas volumes,

blood gases and pH were corrected from the temperature at which they were measured to rectal temperature at the time of sampling.

Blood gas tensions and pH were measured at 37°. Temperature correction factors for P_{O_2} and P_{CO_2} (up to 43°) obtained by *in vitro* tonometry experiments (Warrell, 1969) were similar to others reported in the literature (Bradley, Stupfel & Severinghaus, 1956; Hedley-Whyte & Laver, 1964; Nunn, Bergman, Bunatyan & Coleman, 1965; Kelman & Nunn, 1966). Blood pH was corrected to body temperature using Fig. 6 of Kelman & Nunn's paper (1966). Values for the solubility of O_2 in whole blood were taken from Bartels, Bucherl, Hertz, Rodewald & Shwab (1963) and of CO_2 in plasma from Severinghaus, Stupfel & Bradley (1956). Temperature correction factors for CSF P_{CO_2} and pH and values for the solubility of CO_2 in CSF at different temperatures were taken from Mitchell, Herbert & Carman (1965).

Calculations

Physiological dead space: tidal volume ratio (V_D/V_T) was calculated by the Bohr equation. The alveolar air equation (Fenn, Rahn, & Otis, 1946) was used to calculate 'ideal' alveolar P_{O_2} (P_{A,O_2}) and hence *alveolar-arterial* P_{O_2} *difference* ($PA - a_{O_2}$). Pulmonary venous admixture ($\dot{Q}v_A/\dot{Q}t$) was derived by the shunt equation:

$$\dot{Q}v_A/\dot{Q}_t = \frac{Cc' - a_{O_2}}{Cc' - \bar{v}_{O_2}} \times 100\%$$

$Cc',_{O_2}$, $Ca,_{O_2}$ and $C\bar{v},_{O_2}$ are, respectively, the total O_2 contents (combined and dissolved O_2) of end capillary, arterial, and mixed venous blood. $Ca,_{O_2}$ and $C\bar{v},_{O_2}$ were measured. $Cc',_{O_2}$ was calculated as follows:

$Sc',_{O_2}$ was derived using the digital computer subroutine devised by Kelman (1968); the input (with assumptions in parenthesis) included P_{A,O_2} (= $Pc',_{O_2}$), $Pa,_{CO_2}$ (= $Pc',_{CO_2}$), pHa (= pHc') and T_R (= Tc'). O_2 binding capacity was measured and $Cc',_{O_2}$ was calculated by multiplying this value by $Sc',_{O_2}$. *Residual (anatomical) right to left shunt* ($\dot{Q}s/\dot{Q}t$) was calculated in the same way using values for Cao_2, $C\bar{v}o_2$, $Pa,_{O_2}$, and $Pa,_{CO_2}$ obtained while patients breathed 100% O_2.

Cardiac output ($\dot{Q}_t$) was calculated using the Fick equation. In the calculation of vascular resistances means of the values for $\bar{P}_{BA}$ and $\bar{P}_{PA}$ recorded before and after each collection were used.

Total systemic vascular resistance (TSVR) =

$$\frac{\bar{P}_{BA}\ \text{mmHg}}{\dot{Q}t\ \text{l/min}}$$

Pulmonary vascular inflow resistance (PVIR) =

$$\frac{\bar{P}_{PA}}{\dot{Q}t}$$

RESULTS

The principal findings are presented in Figs. 1–6 and Tables 1–4. Sources of data from healthy subjects at comparable altitudes are given in the legends to each figure. Results from individual patients which are not included here have been deposited with the Librarian, Royal Society

of Medicine (*Clinical Science*, Tables 39/3, 39/4, 39/5, 39/6, 39/7) and are also given by Warrell (1969).

Anthropometric data from the nineteen male patients are shown in Table 1. All had a febrile reaction after tetracycline treatment but there were no deaths in this series and the patients were discharged after 3–10 days.

Chest radiographs. On admission radiographic appearances were normal except in patient 1 (hilar lymphadenopathy), patient 5 (small pleural effusions and a cloudy area in one lung), patient 8 (2 cm ring shadow) and patient 14 (increased vascular markings in both upper lobes). On the next day a 1 cm shadow had appeared in patient 7 and a small pleural effusion in patient 14.

Electrocardiograph. QT interval corrected for rate (QTc) exceeded 0·42 s in 13 patients. This abnormality appeared or became more marked after the rigors in nine patients. ST segment and T wave abnormalities occurred at some stage in all but one patient. There was some shift to the right in mean frontal QRS axis and increased clockwise rotation with evidence of acute right heart strain during or after the rigors in many of the patients; this was particularly marked in patients 10 and 18. P wave voltage increased before the rigors in patients 13 and 18 and afterwards in patients 4 and 6.

Ventilatory capacity (FEV_1, VC, PEF, Table 1) was either normal or restricted before treatment and was unchanged on the day after treatment in the three patients in whom measurements were repeated.

Results of Study 1 (patients 1–6 Table 1)

Body temperature. Values for T_R in the six patients in this study are given in Fig. 1. In the thirteen patients treated conventionally (numbers 1–9, 14–17, Table 1) mean T_R was 40·4° immediately before tetracycline injection. Rigors began about 60 min later and lasted 10–30 min. T_R had risen to a mean of 41·5° when rigors started and reached a peak of 42·0° about 125 min after tetracycline. It then fell to 39·3° 8 h after the rigors and to 37·5° 18 h after the rigors.

Skin temperatures were about 5° below T_R before treatment. In some patients a fall in T_H and/or T_A was seen just before rigors began. During the reaction T_H appeared to rise and fall with systemic arterial pressure, whereas T_A did not rise until the start of the flush phase. Flushing of the hands and sweating were delayed up to 30 min after rigors had ceased. There was little change in ambient temperature during the studies; the range was between 19 and 26°.

Overall gas exchange. CO_2 output ($\dot{V}CO_2$) and O_2 uptake ($\dot{V}O_2$) were high (means: $\dot{V}CO_2$, 380; $\dot{V}O_2$ 505 ml/min STPD) before treatment. They increased strikingly during the rigors (means: $\dot{V}_{CO_2}$, 740; $\dot{V}_{O_2}$, 825 ml/min), returned to pretreatment levels during the flush phase and then declined gradually towards normal values. *Respiratory exchange ratio* (Fig. 2) increased during the rigors to a mean of 0·89, range 0·76–1·01.

Pulmonary ventilation. Total expired ventilation ($\dot{V}_E$) (Fig. 2) was high (mean 13·5 l/min BTPS) before treatment. It increased enormously during the rigors to 20·5–38 l/min. This was achieved by increases in *respiratory frequency* (f) and *tidal volume* (V_T) to means of 36 breaths/min and 850 ml respectively (Table 2). During the flush phase V_T decreased but f remained high. $\dot{V}_E$ declined but its mean remained above 13 l/min until the next morning.

A marked increase in *alveolar ventilation*, $\dot{V}_A$ (Fig. 2) to a mean of 20·8 l/min BTPS accounted for the high $\dot{V}_E$ during the rigors. V_D/V_T and V_D (Table 2) decreased during the rigors in four

TABLE 1. Anthropometric data from the nineteen Ethiopian males with relapsing fever on admission to hospital

Patient number	Age	Height (cm)	Weight (kg)	FEV_1 (l)		VC (l)		FEV_1/VC (%)		PEF (l/min)		Hb (g/100 ml)	PCV (%)
1	19	171	52	2·1	(2·1)*	2·6	(2·5)*	81	(84)*	430	(340)*	12·7	40
2	21	169	54	2·1	(2·0)	3·0	(3·0)	70	(67)	260	(280)	13·0	41
3	20	170	48	1·8	(2·0)	2·3	(2·2)	78	(91)	350	(180)	12·7	40
4	34	172	57	—		—		—		—		14·2	46
5	20	177	60	3·2		3·6		92		440		12·3	39
6	19	172	52	3·0		3·2		94		460		14·4	44
7	19	164	52	1·9		2·3		83		380		12·7	37
8	14	161	39	2·55		3·35		76		240		14·0	44
9	18	159	41	2·0		2·1		95		285		13·0	42
10	15	151	35	2·0		2·1		95		208		12·0	37
11	24	175	63	3·15		3·75		84		600		14·8	44
12	20	170	62	3·35		4·05		80		415		12·9	41
13	22	165	49	2·5		2·8		89		410		12·5	38
14	19	160	50	3·3		4·05		81		400		13·3	39
15	22	159	51	1·9		2·4		79		270		12·5	37
16	20	169	55	1·4		1·5		93		230		13·3	39
17	19	159	49	1·65		1·8		92		390		12·5	37
18	20	166	52									13·0	40
19	15	160	42									13·8	43

* Values obtained on second day of admission.

patients. In four patients values slightly above the normal range (for resting subjects seated upright) were obtained at some time during the reaction.

Acid-base balance. Before treatment Pa,CO_2 (Fig. 3) ranged between 29 and 32 mmHg which is below normal for this altitude. Values fell to between 22·5 and 25·5 mmHg during the rigors and then rose gradually to between 29 and 35·5 mmHg on the next morning. Respiratory

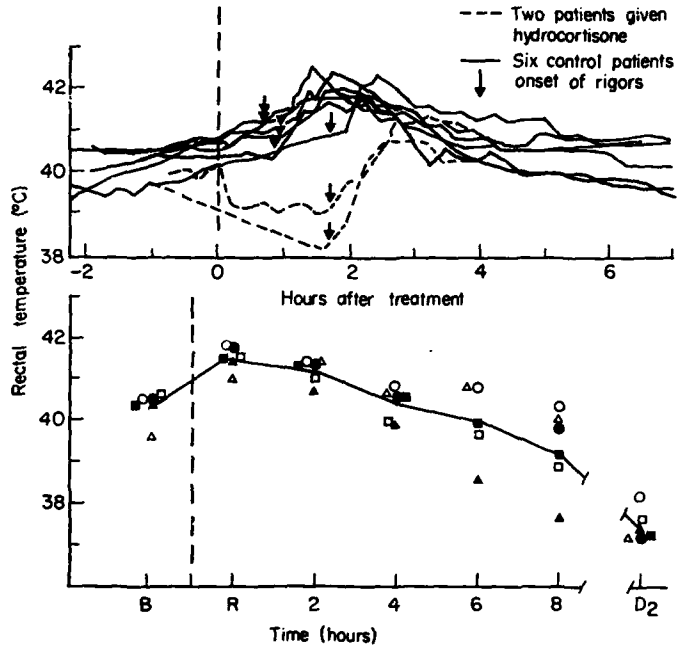

FIG. 1. Rectal temperatures in six patients with relapsing fever (Study 1). Above: serial readings are compared with those from two patients given hydrocortisone infusions (Study 3) starting 1 hour before tetracycline injection. Below: mean values during each of the expired gas collections. Each patient is represented by a separate symbol, ● = 1, ▲ = 2, ○ = 5, △ = 4, ■ = 5, □ = 6. Mean values are joined by a solid line. On the time axis are marked the gas collections before treatment (B), during the rigors (R), 2, 4, 6, and 8 h later and on the next day 18 h after the rigors (D2). The vertical dashed line indicates tetracycline injection.

stimulation caused by arterial puncture on the third day of admission probably explains the fall in Pa,CO_2 and the alkalaemia on that occasion.

HCO_3^-a (Fig. 3) was low before treatment (range 16·1 to 22·6 mmol/l). During the rigors it fell to 13·8–18·1 mmol/l and the mean remained below 18 mmol/l throughout the flush phase. Values were normal the next morning.

Hydrogen ion concentration (H^+a) (Fig. 3) ranged between 37 and 50 n mol/l (pH 7·43–7·30) before treatment. It fell slightly during the rigors and rose gradually during the flush phase. Values for *mixed venous* Pco_2, HCO_3^-, *and* H^+ are given in Table 2. They show the same pattern of changes as the arterial values.

Oxygen transport (Tables 1 and 2). Before treatment arterial *Hb concentration* was 12·3–14·4 g/100 ml and arterial PCV 40 to 46%. These values are below the normal range in Addis

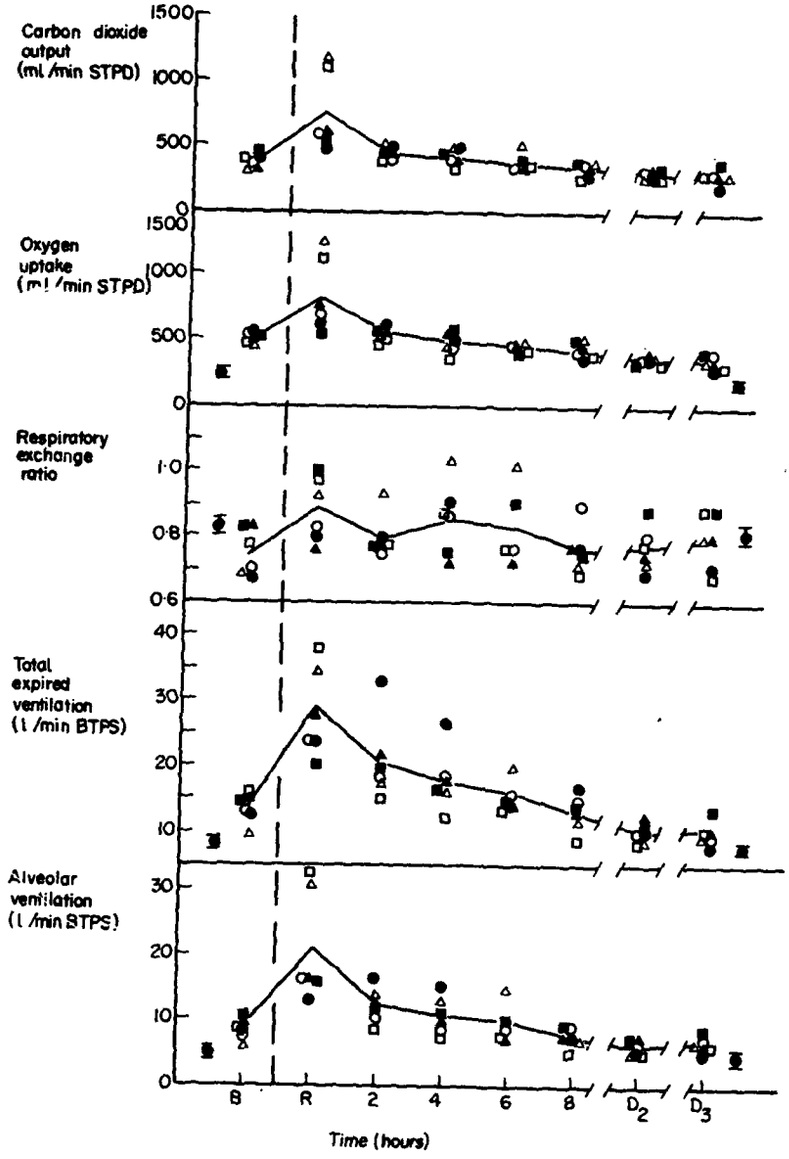

FIG. 2. Overall pulmonary gas exchange and ventilation in six patients with relapsing fever (Study 1). (Key as in Fig. 1.) On the time axis D3 indicates the gas collection on the third day of admission. Normal values at an altitude of 2285 m (mean ± 1 SD) from Chiodi (1963) are given on either side of the figure.

Abeba. During the first 20 h of the study when at least 100 ml of blood were sampled Hb fell by 0·3–2·0 g/100 ml and PCV by 2 to 6%. There was no evidence of haemolysis. *O_2 binding capacity* of Hb was considerably lower than values obtained by the same methods in healthy residents of Addis Abeba.

Pulmonary oxygen uptake. *Pa,O_2* (Fig. 3) ranged between 63 and 74 mmHg before treatment. These values are probably normal for 2285 m. *Pa,O_2* fell during the rigors in two patients but had

TABLE 2. Result of physiological investigations in six patients with relapsing fever (Study 1). Mean values for each physiological variable followed by SD in parentheses before treatment (B); during the rigors (R), 2, 4, 6 and 8 h later (2, 4, 6, 8) and on the second and third days of admission (D2, D3). Individual values are given in a Table deposited with the Librarian at the Royal Society of Medicine.

Variables	B		R		2		4		6	
Respiratory frequency (breaths/min)	24·8	(9·4)	35·7	(10·2)	38·3	(16·2)	32·3	(14·3)	26·0	(5·9)
Tidal volume (ml BTPS)	576	(132)	852	(299)	594	(234)	605	(212)	633	(237)
Physiological dead space (ml BTPS)	150	(31)	173	(40)	162	(28)	150	(26)	163	(23)
Physiological dead space: tidal volume ratio	0·27	(0·05)	0·23	(0·11)	0·29	(0·08)	0·27	(0·08)	0·28	(0·08)
Mixed venous P_{CO_2} (mmHg)	34·5	(1·6)	30·1	(2·8)	29·5	(1·5)	32·5	(1·9)	31·7	(4·3)
Mixed venous HCO_3^- (n mol/l)	19·6	(1·2)	17·9	(1·9)	17·7	(1·3)	18·5	(1·7)	18·1	(2·4)
Mixed venous H^+ (mmol/l)	42·1	(4·8)	40·3	(4·8)	40·5	(5·7)	41·5	(4·2)	42·8	(5·1)
Oxygen binding capacity										
(ml STP/100 ml blood)	15·5	(1·3)	15·1	(1·9)	14·6	(1·1)	14·1	(1·8)	14·1	(1·6)
(ml STP/g haemoglobin)	1·19	(0·08)	1·16	(0·09)	1·14	(0·02)	1·14	(0·05)	1·11	(0·06)
Haemoglobin concentration (g/100 ml)	13·2	(0·9)	13·4	(1·1)	13·0	(0·9)	12·8	(0·9)	12·7	(1·0)
Haematocrit (%)	41·8	(2·5)	41·9	(2·9)	40·5	(3·1)	39·5	(2·9)	38·0	(2·9)
Ideal alveolar P_{O_2} (mmHg)	71·4	(4·5)	82·5	(3·8)	79·7	(3·0)	80·2	(5·5)	78·3	(6·6)
Alveolar-arterial P_{O_2} difference (mmHg)	4·4	(5·4)	13·6	(6·1)	4·8	(5·0)	6·2	(3·4)	8·3	(6·0)
Mixed venous P_{O_2} (mmHg)	39·1	(5·8)	37·7	(4·2)	38·5	(7·3)	36·8	(8·3)	37·0	(7·4)
Mixed venous O_2 saturation (%)	54·2	(7·4)	48·2	(5·3)	52·5	(10·6)	51·1	(10·9)	51·4	(10·3)
Arterial O_2 content (ml STP/100 ml)	13·4	(1·3)	12·8	(2·2)	13·0	(1·3)	12·5	(1·5)	12·4	(1·9)
Mixed venous O_2 content (ml STP/100ml)	8·6	(2·1)	7·4	(1·4)	7·6	(2·9)	7·0	(2·2)	6·8	(2·9)
Arterio-venous O_2 content difference (ml STP/100 ml)	4·8	(1·1)	5·3	(1·1)	5·4	(1·9)	5·6	(1·3)	5·5	(2·0)
Stroke volume (ml)	91	(18)	104	(23)	78	(18)	67	(13)	73	(28)

Variables	8		D2		D3		Normal values		
Respiratory frequency (breaths/min)	27·3	(12·1)	19·9	(3·2)	20·4	(5·2)	17·9	(3·6)	Chiodi (1963)
Tidal volume (ml BTPS)	521	(141)	510	(59)	514	(90)			
Physiological dead space (ml BTPS)	145	(37)	135	(34)	109	(48)			
Physiological dead space: tidal volume ratio	0·28	(0·06)	0·26	(0·06)	0·21	(0·08)	0·24	(0·04)	Warrell & Pope (1969)
Mixed venous P_{CO_2} (mmHg)	35·5	(2·6)	36·6	(1·9)					
Mixed venous HCO_3^- (mmol/l)	19·2	(2·2)	21·4	(2·8)					
Mixed venous H^+ (n mol/l)	44·2	(2·8)	41·2	(2·5)					
Oxygen binding capacity									
(ml STP/100 ml blood)	14·0	(1·3)	13·8	(1·5)	12·8	(1·8)	19·9	(1·1)	Warrell & Pope (1969)
(ml STP/g haemoglobin)	1·13	(0·06)	1·12	(0·05)			1·33	(0·12)	Warrell & Pope (1969)
Haemoglobin concentration (g/100 ml)	12·5	(0·9)	12·2	(1·1)			14·9	(0·7)	Warrell & Pope (1969)
Haematocrit (%)	38·0	(2·9)	37·2	(2·6)			48·8	(2·5)	Warrell & Pope (1969)
Ideal alveolar P_{O_2} (mmHg)	73·6	(6·1)	73·0	(5·2)	76·5	(3·8)	76·0	(3·0)	Warrell & Pope (1969)
Alveolar-arterial P_{O_2} difference (mmHg)	5·6	(5·0)	8·1	(5·4)	12·1	(5·3)	8·6	(2·2)	Warrell & Pope (1969)
Mixed venous P_{O_2} (mmHg)	34·2	(9·8)	32·4	(5·9)					
Mixed venous O_2 saturation (%)	47·1	(11·8)	50·6	(8·8)					
Arterial O_2 content (ml STP/100 ml)	12·1	(1·0)	12·3	(1·4)	11·8	(2·1)	18·6	(0·9)	Warrell & Pope (1969)
Mixed venous O_2 content (ml STP/100 ml)	6·4	(2·9)	6·7	(2·7)					
Arterio-venous O_2 content difference (ml STP/100 ml)	5·8	(2·6)	6·0	(1·8)					
Stroke volume (ml)	78	(29)	73	(26)					

risen in all cases 2 h after the rigors. Subsequently *Pa,O_2* fell as $\dot{V}_A$ declined. $P_A - aO_2$ (Table 2) increased during the rigors to between 8·5 and 22 mmHg. $P\bar{v}O_2$ (Table 2) remained below 40 mmHg throughout the study in three patients.

Sa,O_2 (Fig. 3) was low (82·3 to 89·7%) before treatment. In two patients there was further desaturation during the rigors but in the remainder there was little change. By the next morning all values were approaching the normal range. *$S\bar{v}$,O_2* (Table 2) fell during the rigors in some patients. It remained below 50% throughout the study in three patients.

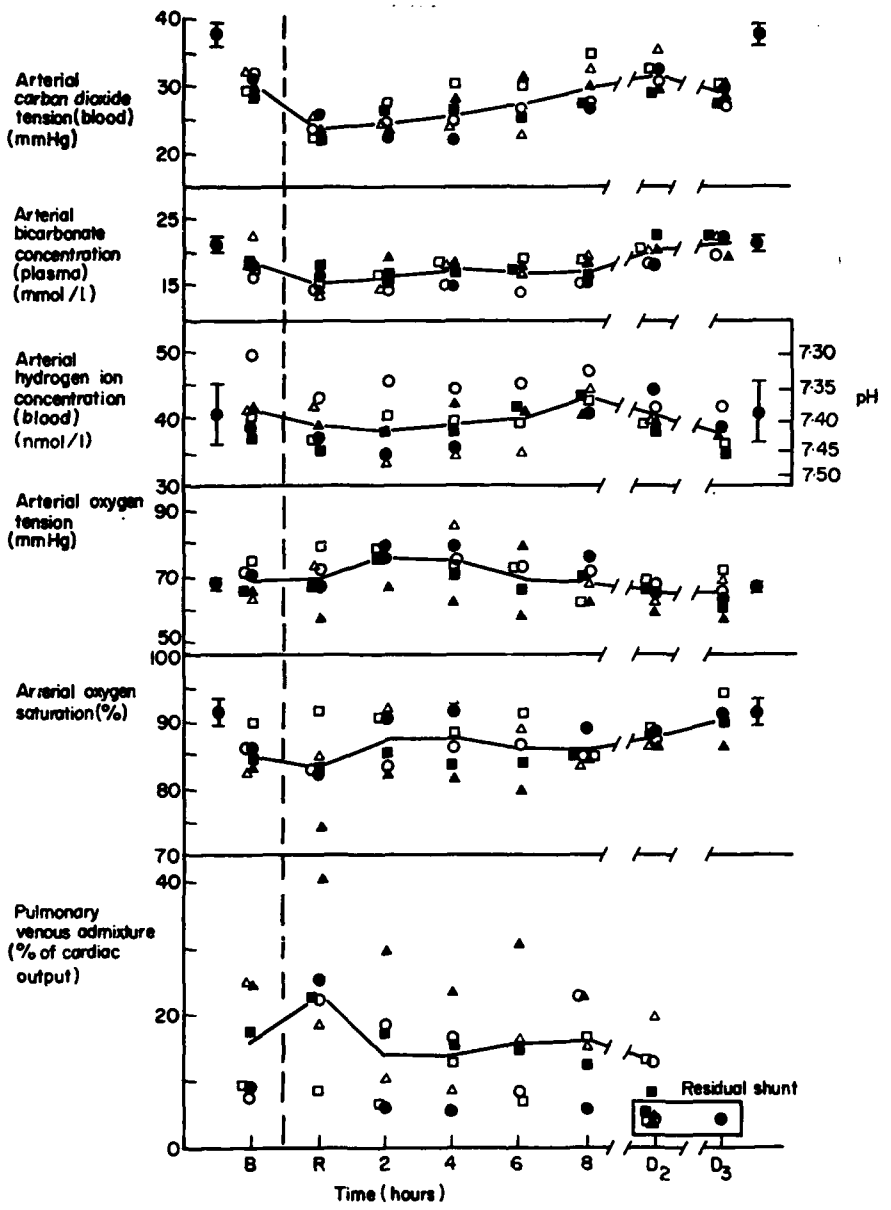

FIG. 3. Blood gas tensions, acid-base composition, oxygen saturation and pulmonary venous admixture in six patients with relapsing fever (Study 1). (Key as in Figs. 1 and 2.) Sources of normal data: Pa,CO_2 and pHa, Chiodi (1963); HCO_3^-a, Hurtado & Aste-Salezar (1948); Pa,O_2 and Sa,O_2, Warrell & Pope (1969).

Ca,O_2 (Table 2) was at all stages considerably lower than values obtained by the same methods in healthy residents of Addis Abeba. Mean $Ca,O_2 - C\bar{v},O_2$ (Table 2) rose gradually from 4·8 ml STP/100 ml before treatment to 6·0 on the next day.

$\dot{Q}VA/\dot{Q}_t$ (Fig. 3) was markedly raised (range 7–25%) before treatment. In most cases it increased during the rigors to between 8 and 40% and then decreased.

$\dot{Q}s/\dot{Q}t$ (on 100% O_2) ranged between 4 and 6% on the second day of admission (Fig. 3). Pa,O_2 ranged between 397 and 436 mmHg.

Cardiac output. $\dot{Q}t$ (Fig. 4) which was about twice the normal resting level before treatment increased further to between 8 and 19·6 l/min during the rigors. During the flush phase it remained above 8 l/min in most cases, but in patients 1 and 5 values below 6 l/min were recorded.

HR (Fig. 4) was between 106 and 131 beats/min before treatment rising to between 123 and 168 beats/min during the rigors and then falling gradually. Calculated *stroke volume* (Table 2) rose slightly during the rigors and fell during the flush phase.

Arterial pressure. In a group of nine patients (numbers 1–9, Table 1) mean $\bar{P}BA$ was 74 (range 57–88) mmHg before treatment. It rose abruptly as rigors began and reached a peak value of 98 (84–121) mmHg. As the rigors ended $\bar{P}BA$ fell sharply and there was persistent hypotension for at least the next 8 h (mean values between 54 and 58 mmHg). Lowest values of between 36 and 71 (mean 48) mmHg recorded between 2 and 9 h after the rigors. $\bar{P}BA$ had risen by the next morning but was still below the normal range.

Mean values of $\bar{P}BA$ for each patient during the collections (Fig. 4) were used to calculate *TSVR* (Fig. 4) which was very low before treatment and decreased further during the rigors reaching its lowest levels 2 h later. It was still below normal on the following morning.

Frequent measurements of $\bar{P}PA$ (Fig. 5) were possible in four patients who breathed room air (numbers 2, 6, 8, and 9, Table 1). Pretreatment values were between 14 and 25 mmHg. In two patients there was an increase in $\bar{P}PA$ before rigors began but in all cases it fell during the rigors reaching minimum values of between 8 and 18 mmHg, 30 to 50 min later. It then rose to between 17 and 33 mmHg which was above the pretreatment levels.

PVIR (Fig. 4) fell during the rigors and rose 4 h later.

Metabolism. Arterial glucose concentration (Fig. 6) rose from between 50 and 169 mg/100 ml before treatment in these fasting patients to a maximum of between 136 and 219 mg/100 ml 6 h after the rigors. *Arterial lactate concentration* (Fig. 6) was 0·49–0·96 mmol/l before treatment. It rose slightly during the rigors in four patients (to 0·68 to 1·44 mmol/l) and subsequently rose in all cases reaching its maximum of between 0·96 and 1·93 mmol/l 4 h after the rigors. *Arterial pyruvate concentration* (Fig. 6) rose during the reaction from 0·04 to 0·09 mmol/l before treatment to reach a maximum of between 0·10 and 0·34 mmol/l 6 h after the rigors.

Results of Study 2 (*patients* 7–9, *Table* 1)

In the three patients in this study cardiorespiratory measurements made during the early part of the febrile reaction confirmed the findings in Study 1.

In patient 7 measurements were made 15 min before rigors began when T_R had risen only 0·6° above the pretreatment values. $\dot{V}CO_2$ and $\dot{V}O_2$ had increased from 425 to 510 and from 525 to 705 ml/min respectively, but pulmonary ventilation was virtually unchanged ($\dot{V}_E$ had increased from 19 to 22·5 l/min and f from 48 to 50 br/min). In contrast $\dot{Q}t$ had increased from 10·5 to 24 l/min. Measurements were repeated 15 min later during the first 3 min of shivering.

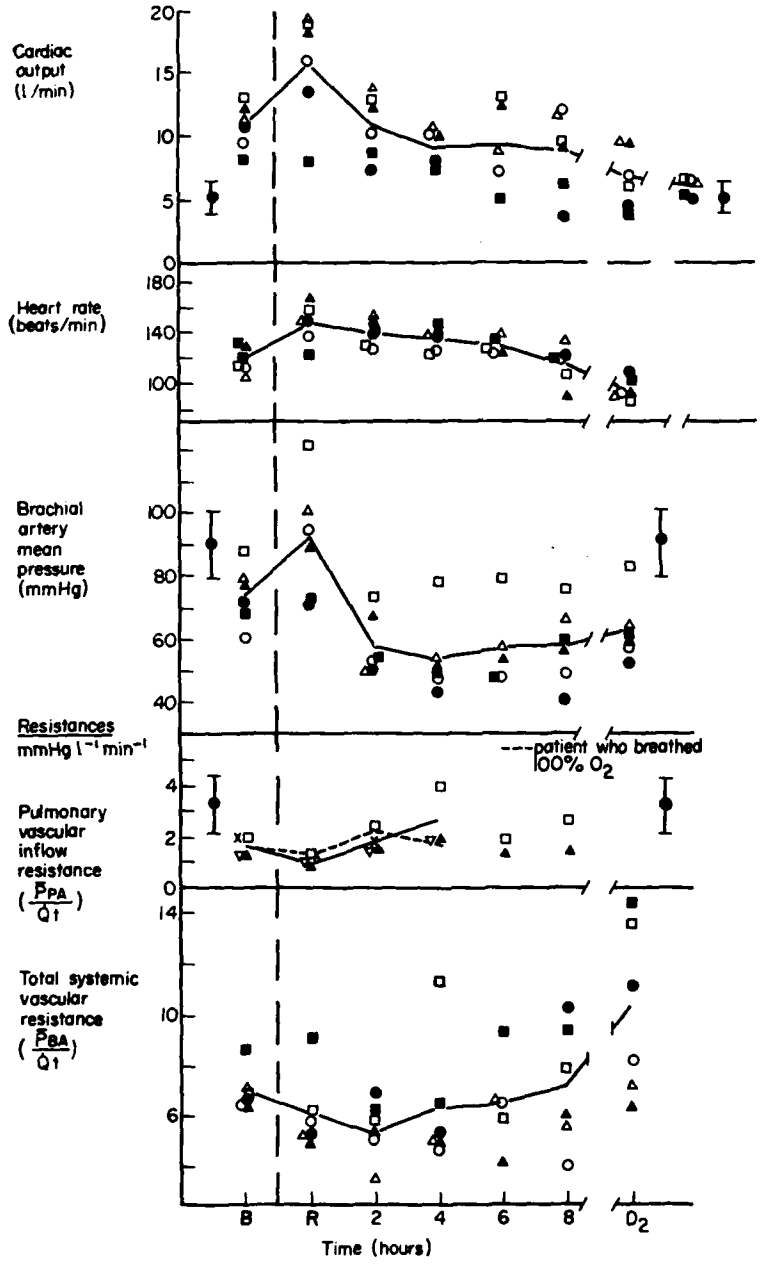

FIG. 4. Haemodynamic data from patients with relapsing fever (Studies 1, 2 and 4). (Key as in Figs. 1 and 2, in addition ▽ = patient 8, and × = patient 9.) Source of normal data: De Micheli *et al.* (1960) N.B. Normal values are for *total* pulmonary vascular resistance.

By this time $\dot{V}O_2$ had increased to 1015 ml/min and $\dot{V}_E$ to 32·5 l/min while $\dot{Q}t$ was 20 l/min. These results suggest that changes in circulation precede those in respiration at the start of the reaction and that the great increases in $\dot{Q}t$ are not entirely due to the muscular activity of shivering.

Measurements were made at the very start of rigors in these patients in an attempt to detect transient changes in TSVR in the early chill phase. In patients 7 and 8 there was a slight increase

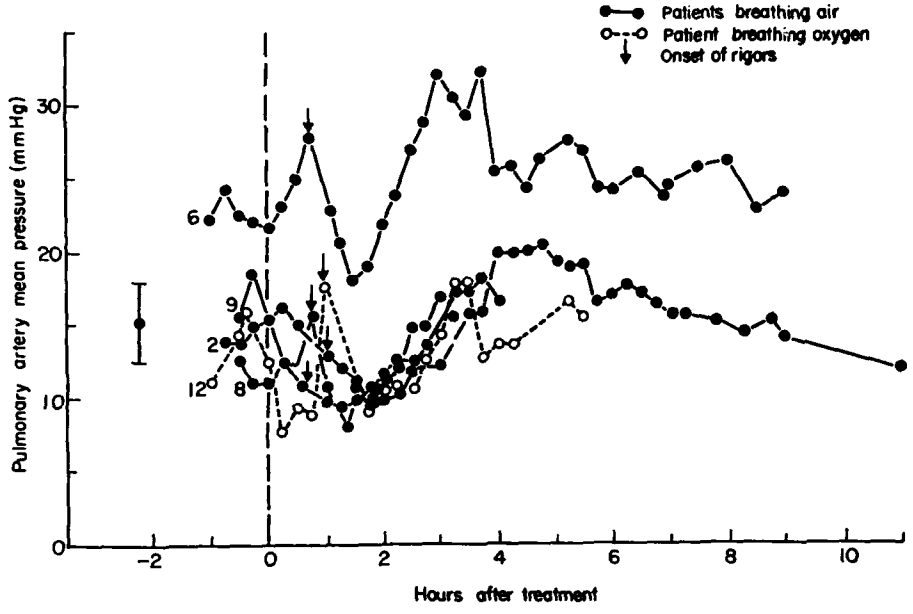

FIG. 5. Serial measurements of pulmonary arterial mean pressure in five patients with relapsing fever (Studies 1, 2 and 4). (Key as in Figs. 1 and 2). Source of normal data: De Micheli *et al.* (1960)

in TSVR at that time (from 3·9 to 5·5, and from 6·8 to 7·5 $mmHg^{-1}$ min^{-1} respectively). Later during the rigors TSVR falls below pretreatment levels (Fig. 4).

Results of Study 3 (*patients* 10 *and* 11, *Table* 1)

In the two patients given hydrocortisone infusions T_R fell from 39·8 and 39·7 (preinfusion) to 39·1 and 38·2 just before rigors began (Fig. 1). Hydrocortisone did not prevent a febrile reaction following tetracycline. Although T_R was 1·6 and 2·2° below the mean value during the rigors in the 6 patients in Study 1 the clinical and physiological changes were no less marked than in that group. During the rigors $\dot{V}O_2$ increased from 320 to 665 and 345 to 1820 ml/min; $\dot{V}_E$ from 9 to 19, and 10 to 50 l/min; $\dot{Q}t$ from 6·5 to 9, and 9 to 17 l/min; and HR from 120 to 142, and 81 to 125 bt/min in patients 10 and 11 respectively.

Results of Study 4 (*patients* 12, 13, 18, *and* 19, *Table* 1)

In Table 3 changes in arterial lactate and pyruvate concentration and lactate/pyruvate ratios in the four patients given O_2 therapy are compared with those in nine control patients (numbers 1–9, Table 1) who breathed room air. In the controls mean lactate rose during the

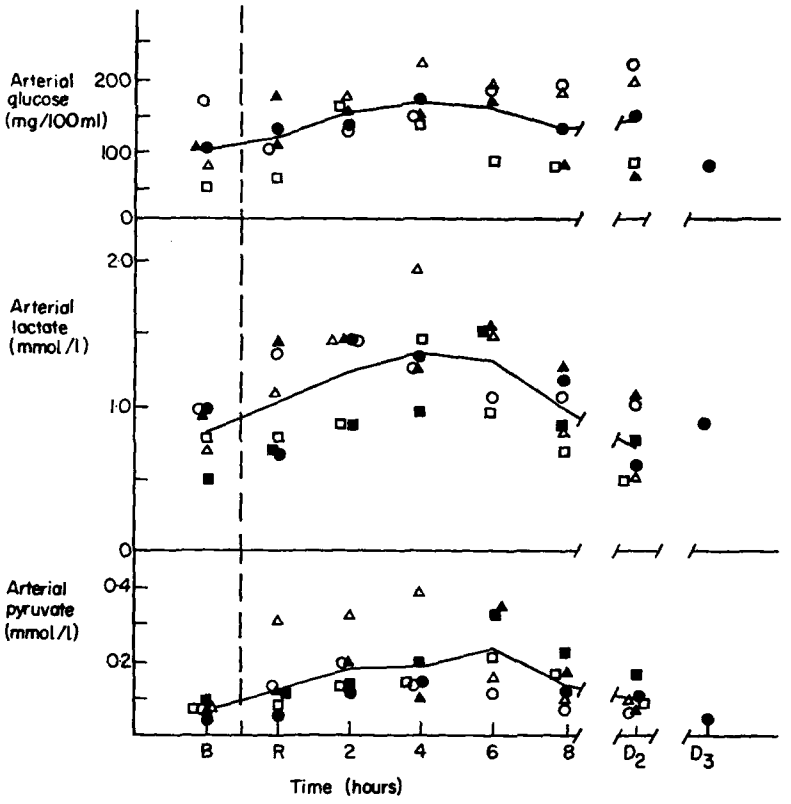

FIG. 6. Arterial glucose, lactate and pyruvate concentrations in six patients with relapsing fever (Study 1). (Key as in Fig. 1).

TABLE 3. Changes in arterial lactate and pyruvate concentrations and lactate/pyruvate ratio from pretreatment levels in nine patients with relapsing fever who breathed air (Studies 1 and 2) compared with values from four patients who breathed oxygen (Study 4). Mean values are given with 1 SD in parentheses. Significance of differences between the two groups at each time is indicated by *P* values

Inspired gas	Change in arterial lactate conc. (mmol/l)		Change in arterial pyruvate conc. (mmol/l)		Lactate/pyruvate ratio	
	Air	Oxygen	Air	Oxygen	Air	Oxygen
Time*						
R	0·24 (0·26)	0·04 (0·15)	0·05 (0·08)	0·03 (0·04)	−2·1 (3·7)	−3·6 (5·0)
	$P > 0·1$		$P > 0·1$		$P > 0·1$	
2	0·44 (0·21)	−0·33 (0·35)	0·11 (0·07)	−0·01 (0·05)	−5·4 (3·3)	−4·5 (5·2)
	$P < 0·0005$		$P < 0·02$		$P > 0·1$	
4	0·45 (0·31)	−0·23 (0·07)	0·11 (0·09)	0·02 (0·05)	−4·9 (4·3)	−6·0 (4·4)
	$P < 0·001$		$P < 0·1$		$P > 0·1$	

* Measurements made during the rigors (R) and 2 and 4 h later (2, 4).

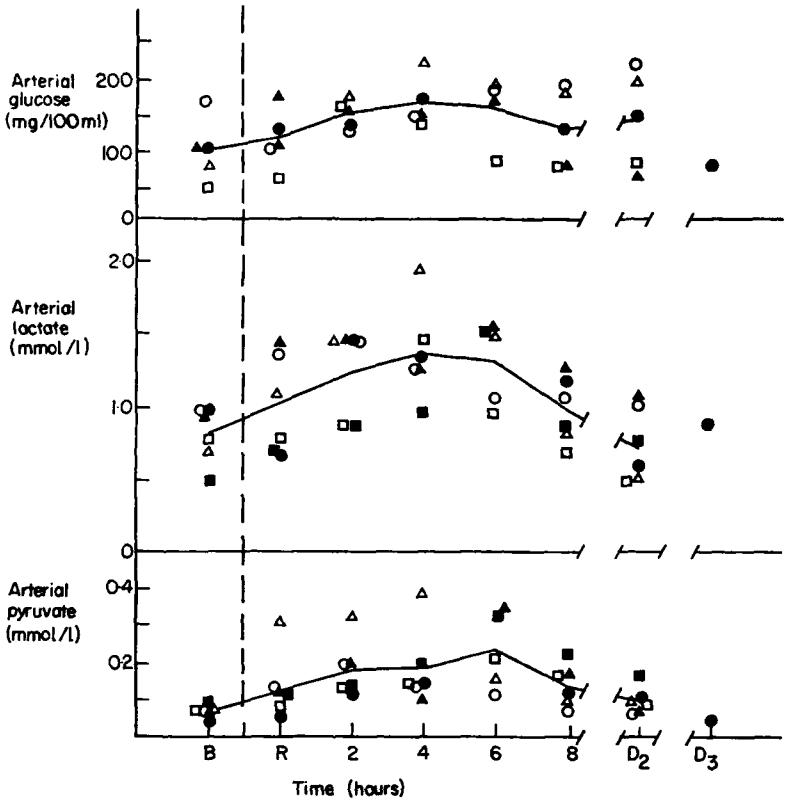

FIG. 6. Arterial glucose, lactate and pyruvate concentrations in six patients with relapsing fever (Study 1). (Key as in Fig. 1).

TABLE 3. Changes in arterial lactate and pyruvate concentrations and lactate/pyruvate ratio from pretreatment levels in nine patients with relapsing fever who breathed air (Studies 1 and 2) compared with values from four patients who breathed oxygen (Study 4). Mean values are given with 1 SD in parentheses. Significance of differences between the two groups at each time is indicated by *P* values

Inspired gas	Change in arterial lactate conc. (mmol/l)		Change in arterial pyruvate conc. (mmol/l)		Lactate/pyruvate ratio	
	Air	Oxygen	Air	Oxygen	Air	Oxygen
Time*						
R	0·24 (0·26)	0·04 (0·15)	0·05 (0·08)	0·03 (0·04)	−2·1 (3·7)	−3·6 (5·0)
	$P>0·1$		$P>0·1$		$P>0·1$	
2	0·44 (0·21)	−0·33 (0·35)	0·11 (0·07)	−0·01 (0·05)	−5·4 (3·3)	−4·5 (5·2)
	$P<0·0005$		$P<0·02$		$P>0·1$	
4	0·45 (0·31)	−0·23 (0·07)	0·11 (0·09)	0·02 (0·05)	−4·9 (4·3)	−6·0 (4·4)
	$P<0·001$		$P<0·1$		$P>0·1$	

* Measurements made during the rigors (R) and 2 and 4 h later (2, 4).

febrile reaction by a maximum of 0·45 mmol/l compared with pretreatment levels but in the patients who breathed O_2 the values fell slightly. The differences between the two groups were statistically significant.

Pyruvate concentration rose slightly in the controls but scarcely changed in the patients who breathed O_2. The change in lactate/pyruvate ratio was the same in both groups.

Arterial glucose concentrations increased in five patients who breathed air (Fig. 6) but not in two who breathed O_2.

In the 2 patients in this study (numbers 12 and 13, Table 1) in whom detailed measurements were made, cardiorespiratory changes during the febrile reaction were found to be as marked as in the control group. During the rigors $\dot{V}O_2$ changed from 500 to 880, and 475 to 560 ml/min; $\dot{V}_E$ from 13 to 24·5, and 14 to 22·5 l/min; $\dot{Q}t$ from 11·5 to 14, and 13 to 10 l/min; and HR from 108 to 143, and 124 to 157 bt/min in patients 12 and 13 respectively. The hypotensive phase after the rigors was the same as in the control group.

In patient 12 $\bar{P}_{PA}$ was measured and PVIR was calculated throughout the febrile reaction. The values were found to be similar to those from the four control patients who breathed air (Figs. 4 and 5).

Results of Study 5 (*patients* 14–17, *Table* 1)

The four patients from whom CSF was sampled had increased respiratory rates (32–44 br/min) before treatment with tetracycline.

The acid-base composition of CSF is compared with that of arterial blood in Table 4. None

TABLE 4. Acid-base composition of lumbar cerebrospinal fluid compared with that of arterial blood sampled simultaneously before treatment (B) from four patients with relapsing fever (Study 5). Arterial blood was sampled again during the rigors (R). Normal paired values for blood and CSF are from subjects at sea level (Semple, 1967).

		P_{CO_2} (mmHg)		HCO_3^- (mmol/l)		pH	
Patient No.	Time	Blood	CSF	Blood	CSF	Blood	CSF
Normal mean ±1 SD		40·8 ±4·0	45·5 ±4·6	25·3 ±2·0	23·2 ±1·5	7·401 ±0·025	7·307 ±0·029
14	B	37·5	37·5	21·1	18·0	7·42	7·33
	R	33		21·6		7·43	
15	B	41·5	44	21·3	18·9	7·35	7·28
	R	36		22·5		7·42	
16	B	27·5	32·5	12·9	19·5	7·32	7·29
	R	24		12·4		7·34	
17	B	27	33·5	16·5	14·9	7·42	7·30
	R	24·5		14·8		7·40	

of the patients was found to have a CSF acidosis. The differences between CSF and blood pH, P_{CO_2}, and HCO_3^- were normal in direction and degree. In no case was the protein or cellular content of the CSF sufficiently high to affect the acid-base calculations.

Following tetracycline treatment the patients developed typical febrile reactions. The changes in T_R, pulse rate, blood pressure and Pa,CO_2 resembled those in the other patients.

DISCUSSION

The patients in these studies were admitted to hospital with high fever which was accentuated during the reaction to treatment with tetracycline. This reaction consisted of distinct phases similar to those described by Altschule *et al.* (1945) in artificially-induced endotoxin fever. During the *prodromal phase* body temperature increased gradually. Changes in heart rate, cardiac output and arterial pressure were detected before rigors began (Study 2). The *chill phase* was characterized by prolonged rigors during which body temperature rose rapidly and metabolic rate doubled. Alveolar ventilation increased excessively and respiratory alkalosis developed but pulmonary venous admixture increased. Systemic arterial mean pressure, cardiac output and heart rate increased and systemic vascular resistance decreased. Pulmonary arterial mean pressure and pulmonary vascular inflow resistance fell. As shivering ceased the *flush phase* began. Systemic arterial pressure fell and remained low for at least the next 8 h. Body temperature reached its peak early in the flush phase and then fell gradually while metabolic rate and pulmonary ventilation declined. Cardiac output remained high in most cases and systemic vascular resistance was very low. Pulmonary arterial mean pressure and inflow resistance increased to above pretreatment levels. Small increases in arterial glucose, lactate and pyruvate concentrations were observed during this phase. The *phase of defervescence* or recovery was detectable within 8 h of the chill phase. Most patients were afebrile 18 h after treatment but pulmonary venous admixture remained high and systemic arterial mean pressure and vascular resistance were low.

Most of the previous studies of cardiorespiratory changes during fever have been concerned with artificially-induced endotoxin fevers in which the rise in body temperature and physiological changes were generally less marked than in the patients with relapsing fever. The most striking findings in the present study were the stimulation of metabolism, ventilation and cardiac output and the abnormalities of acid-base balance, pulmonary oxygen uptake, carbohydrate metabolism and haemodynamics.

Causes of increased metabolism, ventilation and cardiac output

The values for $\dot{V}CO_2$, $\dot{V}O_2$, $\dot{V}_E$ and $\dot{Q}t$ obtained in these studies are among the highest reported in febrile subjects. The low values for Pa,CO_2 indicated that alveolar ventilation was excessive even for the greatly increased metabolic rate, while the low values for $Ca,O_2 - C\bar{v},O_2$ in many cases indicated that $\dot{Q}t$ was also in excess of metabolic requirements. These results agree with those of previous studies (e.g., Grimby, 1962).

In the patients who were given hydrocortisone (Study 3) T_R during the chill phase was considerably below that in the control group (Fig. 1) but their metabolic rate, pulmonary ventilation and cardiac output increased just as much as in the control patients. This suggested that none of these changes was simply related to body temperature, a conclusion also reached by Bradley, Chasis, Goldring & Smith (1945) who found that suppression of endotoxin fever with amidopyrine failed to prevent circulatory changes. Blood sampled during the febrile reaction in LBRF has been shown to contain endotoxin (Bryceson, Cooper, Warrell, Perine & Parry, 1970a). Reinjection of this blood on the day after treatment induced a febrile reaction which was

similar in its respiratory and circulatory manifestations to the original reaction following treatment. These results imply that the exaggerated metabolic respiratory and circulatory responses during the febrile reaction of LBRF represent effects of endotoxin independent of fever itself.

The possibility that hypoxaemia, associated with the high altitude of Addis Abeba, had contributed to the hyperventilation and increased cardiac output was excluded by the observation that oxygen inhalation had no effect on the magnitude of these changes during the febrile reaction (Study 4). Persisting CSF acidosis in the presence of alkalaemia has been observed in a number of clinical conditions in which there is hyperventilation (Cowie, Lambie & Robson, 1962; Semple, 1967), but no CSF acidosis was discovered in the patients with LBRF (Study 5, Table 4). Respiratory infections, acute left ventricular failure with pulmonary oedema, acute haemolysis and hepatic and renal failure have been described in LBRF (Bryceson, Parry, Perine, Warrell, Vukotich & Leithead, 1970b). All are associated with hyperventilation but there was no evidence for their existence in these nineteen patients. Pulmonary embolism would explain some of the findings but the normal physiological dead space and the fall in $\bar{P}_{PA}$ and PVIR during the rigors (Figs. 4 and 5) are against its being the cause of the cardiorespiratory disturbances during the chill phase of the reaction.

Acid-base disturbances

Comparison of the changes in Pa,CO_2, HCO_3^-a and pHa during the rigors with data from voluntarily hyperventilating subjects reveals that the fall in HCO_3^-a was greater than would be expected for the change in pHa (or Pa,CO_2) in uncomplicated respiratory alkalosis (Michel, Lloyd & Cunningham, 1966). This suggests that a metabolic acidosis developed during the rigors. However, Brewin, Gould, Nashat & Neil (1955) found that the CO_2 capacity of haemoglobin (and plasma proteins) increased as temperature was decreased. If the CO_2 capacity of blood proteins were reduced by increasing temperature, the slope of the CO_2 dissociation curve would be made flatter and the inference of metabolic acidosis from the present data would not be justified.

Impaired pulmonary oxygen uptake

Pulmonary venous admixture ($\dot{Q}_{VA}/\dot{Q}t$) was high especially during the rigors when it exceeded 20% in most cases. When 100% oxygen was breathed venous admixture was reduced to within normal limits. This eliminates the possibility of residual (anatomical) shunting and leaves ventilation-perfusion ($\dot{V}/\dot{Q}$) imbalance and impaired pulmonary oxygen diffusion as the possible causes of high $\dot{Q}_{VA}/\dot{Q}t$. Against $\dot{V}/\dot{Q}$ imbalance was the normal physiological dead space and the absence of radiographical evidence of a pulmonary lesion which might have distorted $\dot{V}/\dot{Q}$ relationships. The combination of high $\dot{V}O_2$, low P_{A,O_2}, high pulmonary blood flow and possibly reduced pulmonary capillary blood volume (see below) may have caused diffusion to become the limiting factor in pulmonary oxygen uptake. The diffusing capacity of the lung for oxygen is reduced by decreasing blood oxygen binding capacity (Staub, Bishop & Forster, 1962) which was very low in all the patients with LBRF (Table 2).

At present the contribution of impaired diffusion and $\dot{V}/\dot{Q}$ abnormalities to an observed $\dot{Q}_{VA}/\dot{Q}t$ and $P_A{}^-aO_2$ cannot be quantitated, but there are reasons for suspecting that pulmonary oxygen uptake was limited by diffusion in these patients with LBRF.

Haemodynamic changes

As the rigors abated there was a dramatic fall in $\bar{P}_{BA}$ which generally remained below 60 mmHg for at least the next 8 h (Fig. 4). Since $\dot{Q}t$ remained high (above 8 l/min) in most cases hypotension was clearly due to low TSVR. The profound fall in systemic vascular resistance, which is a well recognized feature of the flush phase of the endotoxin reaction, is due mainly to renal and splachnic vasodilation (Chasis, Ranges, Goldring & Smith, 1938; Bradley & Conan, 1947). In our patients $\bar{P}_{BA}$ and TSVR were still low 18 h after the rigors. This could have been due to some persisting action of endotoxin or the humoral mediator of vasodilatation (Cranston, Vial & Wheeler, 1959) which altered the responsiveness of the vasculature to the mechanisms which normally control blood pressure.

$\bar{P}_{PA}$ fell together with PVIR during the rigors and the early part of the flush phase (Fig. 5). This change may have resulted from reduction in pulmonary blood volume due to pooling of blood in areas of the systemic circulation dilated by endotoxin. A few hours after the rigors, while systemic arterial pressure and resistance remained low, $\bar{P}_{PA}$ and PVIR increased to above their pretreatment levels (Figs. 4 and 5). Moser, Perry & Luchsinger (1963) also observed increases in $\bar{P}_{PA}$ while $\bar{P}_{BA}$ was falling during the flush phase in human subjects and Kuida, Hinshaw, Gilbert & Visscher (1958) described similar changes in dogs and cats given lethal doses of endotoxin. These late increases of $\bar{P}_{PA}$ and PVIR in LBRF were possibly the result of redistribution of blood volume from the systemic to the pulmonary circulation. Alternative explanations include pulmonary embolization by clumps of agglutinating spirochaetes (Parry, Warrell, Perine, Vukotich & Bryceson, 1970), pulmonary vascular occlusion by sequestrated leucocytes (Schofield, Talbot, Bryceson & Parry, 1968), pulmonary vasoconstriction caused by a humoral agent (Kuida *et al.*, 1958) and left ventricular failure (Parry *et al.*, 1967). Our observation that oxygen inhalation did not prevent the late increases in $\bar{P}_{PA}$ and PVIR (Figs. 4 and 5) suggests that these changes were not attributable to the low inspired P_{O_2} at 2285 m.

Carbohydrate metabolism

Arterial glucose, lactate and pyruvate concentrations increased during the febrile reaction reaching peak values 4–6 h after the rigors (Fig. 6). The increases in lactate were relatively small but were seen in all the patients who breathed air. Lactate/pyruvate ratios fell during the reaction and glucose concentration increased suggesting a general stimulation of carbohydrate metabolism rather than excessive anaerobic metabolism. But the four patients who inhaled oxygen throughout the reaction (Study 4) showed no increases in glucose, lactate or pyruvate concentrations which suggests that the changes observed in the patients who breathed air were due directly or indirectly to hypoxia. Although total blood flow was high in most patients flow to some regions may have been inadequate because of diversion of blood to the dilated renal and splanchnic areas. A defect in blood oxygen transport in our patients was suggested by low oxygen binding capacities which would contribute to tissue hypoxia.

The hyperlactataemia resulting from respiratory alkalosis (Huckabee, 1958) is associated with increased lactate/pyruvate ratio (Eldridge & Salzer, 1967), but in our patients this ratio decreased and the increases in lactate were unimpressive during the chill phase when respiratory alkalosis was most marked. Increased catecholamine secretion could have contributed to the increases in glucose, lactate and pyruvate concentrations, the high metabolic rate and the circulatory and respiratory changes. Oxygen therapy may have prevented the changes in

carbohydrate metabolism indirectly, by reducing the stimulus to endogenous catecholamine secretion.

Therapeutic implications

All drugs which effectively eliminate spirochaetes from the blood and prevent relapses are capable of producing febrile reactions of the type described above (Bryceson *et al.*, 1970b). Taft & Pike (1945) and Bryceson *et al.* (1970b) were unable to find doses or modes of administration of penicillin or tetracycline which were both therapeutically effective and appreciably reduced the severity of the reaction. This has also been the experience with penicillin treatment and the Jarisch–Herxheimer reaction of syphilis (*British Medical Journal*, 1967).

Corticosteroids can ameliorate the Jarisch–Herxheimer reaction of syphilis (Graciansky & Grupper, 1961; Gudjonsson & Skog, 1968) and the very similar febrile reaction which follows the treatment of brucellosis melitensis with tetracycline (Magill, Killough & Said, 1954). In our patients with LBRF, however, the infusion of 20 mg of hydrocortisone kg^{-1} h^{-1} suppressed fever initially but did not prevent the reaction following treatment. These observations might be explained by differences in the quantity of endotoxin present before and during the reactions in each of the two diseases. It remains possible that even larger doses of corticosteroid might have prevented the reaction, but these would not be justified because of the bleeding tendency in patients with LBRF (Bryceson *et al.*, 1970b).

Most of the deaths during the febrile reaction of LBRF have occurred after the development of circulatory collapse (Robertson, 1932; Chung & Chang, 1939; Wolff, 1946; Bryceson *et al.*, 1970b). Since none of the patients in the present study died the immediate causes of death during the reaction to treatment remain uncertain, but trends were observed which might have caused death had they progressed.

During the prolonged flush phase systemic blood pressure was low because of low vascular resistance resulting, presumably, from splanchnic and renal vasodilatation by endotoxin. In this situation systemic arterial pressure may be kept up only by maintaining a high cardiac output. In most of our patients $\dot{Q}t$ was above 8 l/min and $\bar{P}_{BA}$ was above 50 mmHg throughout the flush phase, but in the two patients (numbers 1 and 5) in whom $\dot{Q}t$ fell below 6 l/min. $\bar{P}_{BA}$ fell below 50 mmHg (Fig. 4) and $Ca\text{-}\bar{v}O_2$ increased to 10 and 8·5 ml/100 ml indicating that $\dot{Q}t$ was inadequate for metabolic requirements.

Cardiac failure and extracellular fluid (ECF) volume depletion may jeopardize the maintenance of a high cardiac output during this critical period. Parry *et al.* (1967) observed acute cardiac failure with pulmonary oedema during the hypotensive phase of the reaction. This was effectively treated with parenteral digoxin in several cases but measures aimed at reducing circulating blood volume (diuretics, venesection etc.) would be disastrous because of the low systemic resistance. The ECG evidence of myocardial damage in patients with LBRF (Parry *et al.*, 1970) is consistent with the myocarditis found post mortem (Anderson & Zimmerman, 1955). The development of primary pump failure due to myocarditis would obviously prevent the maintenance of a high $\dot{Q}t$.

ECF volume depletion is an expected complication of prolonged high fevers such as LBRF during which there is profuse sweating, increased evaporation from the hot over-ventilated respiratory tract and failure to drink. A similar situation has been recognized in marathon runners (Pugh, Corbett & Johnson, 1967; Pugh, personal communication). The intravenous administration of at least 1 litre of normal saline to each of our patients prevented severe hypo-

tension due to ECF volume depletion, but we have seen patients who developed hypotension without signs of cardiac failure and were successfully treated by infusing normal saline (Bryceson *et al.*, 1970b). Central venous pressure should be measured to control the rate of intravenous infusions.

The observation that some metabolic abnormalities of the flush phase were reduced or prevented by oxygen therapy may encourage the use of oxygen therapy during the reaction especially in severe cases at high altitudes.

Jarisch–Herxheimer-like reactions have been described in a large number of diseases other than LBRF and syphilis (Warrell, 1969). The possible mechanisms under-lying these reactions have been discussed by Bryceson (1970). The physiological changes described here would support the hypothesis that the sudden release of endotoxin gives rise, directly or indirectly through other mediators, to all the features of the febrile reaction which follows treatment of LBRF.

The results of these studies indicate the magnitude of the physiological disturbances which may accompany infective fevers, and emphasize the physiological stresses to which feverish patients are subjected. These findings may influence the management of patients with LBRF but they may also have a more general relevance to the understanding of the physiological effects of fevers caused by infection.

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